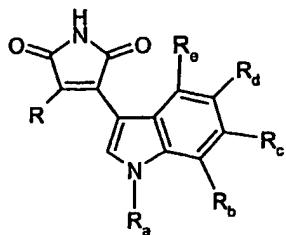


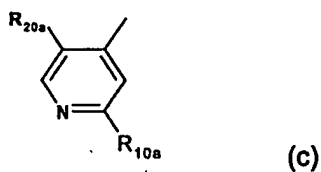
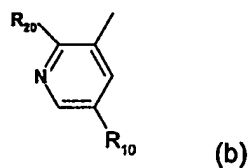
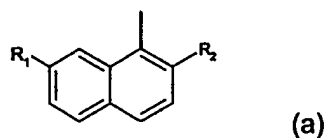
## CLAIMS

1. Use of a compound which is an inhibitor of PKC, in free form or in a pharmaceutically acceptable salt form, for the manufacture of a medicament for treating or preventing diseases or disorders mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer, wherein said compound possesses a selectivity for PKC $\alpha$ , PKC $\beta$  and optionally PKC $\theta$ , over one or more of the other PKC isoforms of at least 10 fold, as measured by the ratio of the IC<sub>50</sub> of the compound for a PKC which is not  $\alpha$  and  $\beta$ , and optionally not  $\theta$ , to the IC<sub>50</sub> of the compound for the PKC $\alpha$ , PKC $\beta$  or PKC $\theta$ , respectively.
2. A compound which is an inhibitor of the PKC, in free form or in a pharmaceutically acceptable salt form, wherein said compound possesses a selectivity for the PKC over one or more protein kinases which do not belong to the CDK-family, and a selectivity for the PKC $\alpha$ , PKC $\beta$  and optionally PKC $\theta$ , over one or more of the other PKC isoforms of at least 10 fold, as measured according to claim 1.
3. A compound which is an inhibitor of the PKC, in free form or in a pharmaceutically acceptable salt form, wherein said compound possesses a selectivity for PKC $\alpha$ , PKC $\beta$  and optionally PKC $\theta$ , over one or more of the other PKC isoforms of at least 10 fold, and for which the ratio of the IC<sub>50</sub> value as determined by Allogeneic Mixed Lymphocyte Reaction (MLR) assay to the IC<sub>50</sub> value as determined by Bone Marrow proliferative (BM) assay is higher than 5.
4. A compound which is an inhibitor of the PKC, in free form or in a pharmaceutically acceptable salt form, wherein said compound possesses a selectivity for the PKC $\alpha$ , PKC $\beta$  and PKC $\theta$ , over one or more of the other PKC isoforms of at least 10 fold, as measured according to claim 1.
5. A compound of formula I



wherein

$R_a$  is H;  $C_{1-4}$ alkyl; or  $C_{1-4}$ alkyl substituted by OH,  $NH_2$ ,  $NHC_{1-4}$ alkyl or  $N(di-C_{1-4}alkyl)_2$ ;  
one of  $R_b$ ,  $R_c$ ,  $R_d$  and  $R_e$  is halogen;  $C_{1-4}$ alkoxy;  $C_{1-4}$ alkyl;  $CF_3$  or CN and the other three  
substituents are each H; or  $R_b$ ,  $R_c$ ,  $R_d$  and  $R_e$  are all H; and  
 $R$  is a radical of formula (a), (b) or (c)



wherein

$R_1$  is  $-(CH_2)_n-NR_3R_4$ ,

wherein

each of  $R_3$  and  $R_4$ , independently, is H or  $C_{1-4}$ alkyl; or  $R_3$  and  $R_4$  form together with the  
nitrogen atom to which they are bound a heterocyclic residue;

$n$  is 0, 1 or 2; and

$R_2$  is H; halogen;  $C_{1-4}$ alkyl;  $CF_3$ ; OH; SH;  $NH_2$ ;  $C_{1-4}$ alkoxy;  $C_{1-4}$ alkylthio;  $NHC_{1-4}$ alkyl;  $N(di-C_{1-4}alkyl)_2$ , CN, alkyne or  $NO_2$ ;

wherein

each of  $R_{10}$  and  $R_{10a}$ , independently, is a heterocyclic residue; or a radical of formula  $\alpha$



wherein X is a direct bond, O, S or NR<sub>11</sub> wherein R<sub>11</sub> is H or C<sub>1-4</sub>alkyl,

R<sub>7</sub> is C<sub>1-4</sub>alkylene or C<sub>1-4</sub>alkylene wherein one CH<sub>2</sub> is replaced by CR<sub>x</sub>R<sub>y</sub> wherein one of R<sub>x</sub> and R<sub>y</sub> is H and the other is CH<sub>3</sub>, each of R<sub>x</sub> and R<sub>y</sub> is CH<sub>3</sub> or R<sub>x</sub> and R<sub>y</sub> form together -CH<sub>2</sub>-CH<sub>2</sub>-,

Y is bound to the terminal carbon atom and is selected from OH, -NR<sub>30</sub>R<sub>40</sub> wherein each of R<sub>30</sub> and R<sub>40</sub>, independently, is H, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl, aryl-C<sub>1-4</sub>alkyl, heteroaryl-C<sub>1-4</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>1-4</sub>alkyl optionally substituted on the terminal carbon atom by OH, halogen, C<sub>1-4</sub>alkoxy or -NR<sub>50</sub>R<sub>60</sub> wherein each of R<sub>50</sub> and R<sub>60</sub>, independently, is H, C<sub>1-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-4</sub>alkyl, aryl-C<sub>1-4</sub>alkyl, or R<sub>30</sub> and R<sub>40</sub> form together with the nitrogen atom to which they are bound a heterocyclic residue; and

each of R<sub>20</sub> and R<sub>20a</sub>, independently, is H; halogen; C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkoxy; CF<sub>3</sub>; nitrile; nitro or amino;

or a salt thereof.

6. A compound according to claim 5 wherein R<sub>a</sub> is H or methyl; each of R<sub>2</sub>, R<sub>20</sub> and R<sub>20a</sub>, independently, is H, Cl, NO<sub>2</sub>, F, CF<sub>3</sub> or methyl, n is 0 or 1; one of R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub> and R<sub>e</sub> is methyl or ethyl and the other three substituents are H; or R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub> and R<sub>e</sub> are all H; and each of R<sub>3</sub> and R<sub>4</sub>, independently, is H, methyl, ethyl or *i*-propyl; or R<sub>3</sub> and R<sub>4</sub> form together with the nitrogen atom to which they are bound a heterocyclic residue optionally substituted; and each of R<sub>1</sub>, R<sub>10</sub> and R<sub>10a</sub>, independently, is a heterocyclic residue.

7. A compound according to claim 5 or 6 which is selected from

3-[5-Chloro-2-(4-methyl-piperazin-1-yl)-pyridin-4-yl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione;  
 3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;  
 3-(7-Aminomethyl-2-Chloro-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;  
 3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;  
 3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;  
 3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;  
 3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(6-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-methylaminomethyl-naphthalen-1-yl)-4-(5-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(6-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-dimethylaminomethyl-naphthalen-1-yl)-4-(5-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-{2-Chloro-7-[(ethyl-methyl-amino)-methyl]-naphthalen-1-yl}-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-diethylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-ethylaminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-[2-Chloro-7-(isopropylamino-methyl)-naphthalen-1-yl]-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-[2-Chloro-7-(4-methyl-piperazin-1-ylmethyl)-naphthalen-1-yl]-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(2-Chloro-7-pyrrolidin-1-ylmethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(1,7-dimethyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-2-methyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Aminomethyl-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Amino-naphthalen-1-yl)-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Amino-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-Dimethylaminomethyl-2-fluoro-naphthalen-1-yl)-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;

3-(7-dimethylaminomethyl-2-fluoro-naphthalen-1-yl)-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

3-(1-Methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrrole-2,5-dione;

3-(1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrrole-2,5-dione;

3-(7-methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-pyridin-3-yl]-pyrrole-2,5-dione;  
3-(1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-pyridin-3-yl]-pyrrole-2,5-dione;  
3-(1-methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-pyridin-3-yl]-pyrrole-2,5-dione;  
3-(7-methyl-1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrrole-2,5-dione;  
3-(1H-indol-3-yl)-4-[5-(4-methyl-piperazin-1-yl)-2-nitro-pyridin-3-yl]-pyrrole-2,5-dione;  
3-[2-chloro-5-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-4-(7-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;  
3-(1H-indol-3-yl)-4-[5-methyl-2-(4-methyl-piperazin-1-yl)-pyridin-4-yl]-pyrrole-2,5-dione;  
3-(1H-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-5-nitro-pyridin-4-yl]-pyrrole-2,5-dione;  
3-(1H-indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-pyridin-4-yl]-pyrrole-2,5-dione; in free form or in a pharmaceutically acceptable salt form.

8. A compound according to any one of claims 5 to 7, in free form or in a pharmaceutically acceptable salt form, for use as a pharmaceutical.

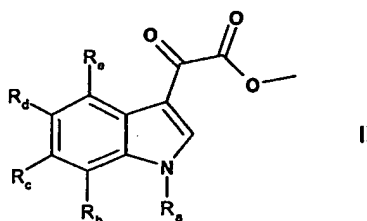
9. A compound according to any one of claims 2 to 7, for treating or preventing diseases or disorders mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer.

10. A pharmaceutical composition comprising a compound according to any one of claims 2 to 7, in free form or in pharmaceutically acceptable salt form, in association with a pharmaceutically acceptable diluent or carrier therefor.

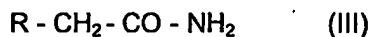
11. Use of a compound according to any one of claims 2 to 7, in free form or in a pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 10 in the manufacture of a medicament for treating or preventing diseases or disorders mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer.

12. A pharmaceutical combination comprising a compound according to any one of claims 2 to 7, in free form or in a pharmaceutically acceptable salt form, and a further agent selected from immunosuppressant, immunomodulatory, anti-inflammatory, chemotherapeutic, antiproliferative and anti-diabetic agents.

13. A process for the production of a compound according to claim 5 or 6, which process comprises reacting a compound of formula II



wherein  $R_a$  to  $R_e$  are as defined in claim 5,  
with a compound of formula III



wherein R is as defined in claim 5,

and, where required, converting the resulting compound of formula I obtained in free form to a salt form or vice versa, as appropriate.

14. A method for treating or preventing disorders or diseases mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of an inhibitor of PKC which possesses a selectivity for PKC $\alpha$ , PKC $\beta$  and optionally PKC $\theta$ , over one or more of the other PKC isoforms of at least 10 fold, as measured according to claim 1, or a pharmaceutically acceptable salt thereof.

17. A method for treating or preventing disorders or diseases mediated by T lymphocytes and/or PKC, in particular allograft rejection, graft versus host disease, autoimmune diseases, infectious diseases, inflammatory diseases, cardiovascular diseases or cancer, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of a compound according to any one of claims 2 to 7, or a pharmaceutically acceptable salt thereof.